Burden of bacterial antimicrobial resistance among hospitalised patients in Spain: findings from three nationwide prospective studies

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Summary

Background Assessing the burden of antimicrobial resistance is essential to determine the magnitude of this problem and to set its priority. We aimed to estimate the burden of disease caused by multidrug-resistant microorganisms (MDRO) in hospitalised patients in Spain.

Methods Three prospective nationwide studies were conducted in 2018, 2019 and 2023. All patients with a new diagnosis of infection with any of 10 selected MDROs plus *Clostridioides difficile* during the study period (one week in 2018 and 2019 and two weeks in 2023) were included. Patient demographic, and clinical outcomes were analysed, including incidence, crude all-cause 30-day mortality and years of life lost (YLL). These results were used to calculate weighted and seasonally adjusted annual estimates for the whole country.

Findings In total, 82, 133 and 130 centres participated in the study in 2018, 2019 and 2023, respectively, recording a total of 907, 1392 and 2351 MDRO infections, representing a weighted incidence density of 3.54 (95% CI 2.92–4.17), 5.01 (3.95–6.07), and 4.41 (3.55–5.27) cases/1000 stays, respectively. A total of 161, 198 and 352 patients died with an MDRO infection, representing a weighted incidence density of 0.46 (0.16–0.76), 0.43 (0.17–0.69), and 0.62 (0.52–0.72)

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deaths/1000 stays, respectively. Based on these data, a nationwide occurrence of 155,294 MDRO infections (95% CI 127,928–182,569) with 20,065 deaths (6938–32,958) was estimated for 2018, 210,451 MDRO infections (165,963–254,975) with 17,982 deaths (7071–28,700) for 2019, and 173,653 MDRO infections (139,814–207258) with 24,582 deaths (20,461–28,796) for 2023.

Interpretation The burden of disease caused by MDRO infections among hospitalised patients in Spain is very high and remains stable over the study period. National actions to combat bacterial resistance need to be intensified.

Funding The management costs of this study were funded by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). Researchers have participated voluntarily and none of the investigators received funding for conducting the study.

Keywords: Antimicrobial resistance; Infections; Burden; Hospital; Spain

Research in context

Evidence before this study

Multidrug-resistant microorganism (MDRO) infections cause a high burden of disease and are one of the greatest threats to global public health, but the magnitude of their impact is not easy to measure because these infections are so frequent and diverse. Different studies at local, national and international levels have been carried out to try to measure the health burden they represent. We searched PubMed for those articles published before May 20, 2024, using the search terms "burden" and "antimicrobial resistance" or "antibiotic resistance", in addition to the terms "prospective" or "cohort" and "national" or "country", with no date or language restrictions. Most of them make estimates based on retrospective studies from different databases, usually from MDRO isolates through the microbiology laboratory, and the cases identified lack clinical follow-up, so the type of infection and the actual outcome is not known with certainty. The results obtained in the different studies are very disparate and their quality is generally limited. A more precise understanding of the health problem of MDRO infections at a nationwide scope is needed.

Added value of this study

To our knowledge, this study provides the most comprehensive analysis of the annual burden of AMR in Spain to date and contains methodological advances over previous related work. The main added value of this study is that the health burden caused by MDRO infections in this country is much higher than previously described. This study adds a new and efficient approach to measure the health burden of MDRO infections in a country, through an incidence study on a highly representative number of hospitals over a limited period, with prospective follow-up of all patients with a new MDRO infection, conducted jointly by microbiologists and clinicians. These observed data have been used to make weighted and seasonally adjusted annual countrywide estimations. The estimates obtained in this way are consistent because the study has been repeated with the same method three times with comparable results. This shows that it is a feasible and consistent study. Moreover, the methodology of our study can be used in other countries for comparative purposes.

Implications of all the available evidence

Our estimates indicate that AMR in hospitalised patients is a serious health problem in Spain, greater than previously estimated, which remains stable despite the interventions that have been carried out and therefore are not sufficient. These data can be useful to raise awareness of this problem among health professionals, the media, citizens and health authorities. It can also help health authorities to prioritise resources according to the magnitude of the AMR problem. And for healthcare professionals, to better understand the main epidemiological, microbiological and clinical characteristics of MDROs in hospitalised patients and thus design the best interventions to improve outcomes. Finally, the time-efficient methodology of this study could be useful to measure the health burden of MDROs in other European countries and to compare results.

Introduction

Infections caused by multidrug-resistant microorganisms (MDRO) are one of the most important threats to public health worldwide.[1] The outcomes of patients with MDRO infections are worse than those of the same infections when caused by susceptible bacteria, including increased mortality, hospital stay, and healthcare costs.[2] Previous estimations suggested that, if no action is taken, they will be the leading cause of death in the world by 2050.[3]

Determining the current and projected impact of antimicrobial resistance (AMR) is critical to help

policymakers allocate resources and inform action plans against AMR.[4] The disease burden of these infections is difficult to assess, and significant variations have been observed between studies conducted by different institutions and countries. A study by the European Centre for Disease Prevention and Control (ECDC) estimated that, in 2015, there were 671,689 infections caused by MDRO in the European Union and European Economic Area, accounting for 33,110 attributable deaths.[5] Other two recent studies estimated the attributable deaths to MDRO in 2019: one estimated 73,700 in central Europe, eastern Europe and central Asia[6] and the other, 133,000 in the WHO European region.[7] In France, annual estimated deaths reached 12,500[8] and, in Spain, different studies performed between 2015 and 2019 estimated from 1900 to 6220 yearly deaths.[5,9,10] The consequences of AMR in Europe, specifically those caused by bloodstream infections (BSIs) due to six selected pathogens, have been assessed by a systematic review, concluding that multidrug-resistant BSIs are associated with increased mortality.[11] Information from low and middle-income countries is very limited.[12,13]

Although those retrospective studies analysed the mortality of patients with MDRO infections, none of them performed an individualized clinical follow-up for a period of time.[5–10] The heterogeneity of data sources and methodological approaches used in these studies may elucidate the observed discrepancies.[7,14,15] Thus, in the study for the WHO European region, data were retrieved from a wide range of international stakeholders, including research hospitals, surveillance networks, and infection databases maintained by private laboratories and medical technology companies.[7] A more precise understanding of the magnitude of the health challenge posed by MDRO infections and the development of new methods to measure it are needed.

To address this goal, the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC), in collaboration with two of its study groups, GEMARA (Antimicrobial Resistance and Mechanisms of Action Study Group) and GEIRAS (Healthcare Associated Infections Study Group), designed and conducted a nationwide prospective multicentre incidence study with the aim of quantifying and defining the annual burden of disease caused by MDRO.

Methods

Study design and setting

We designed a prospective multicentre study in Spanish hospitals, during three consecutive years: 2018, 2019 and 2020. The latter, which could not be carried out due to the SARS-CoV-2 pandemic, was finally conducted in 2023. An invitation to participate in the study was emailed to all over 3500 SEIMC members. Hospitals were eligible if at least one microbiologist and one infectious disease physician accepted to participate as local research team to be responsible for the collection of microbiological and clinical data through digital medical records and, when necessary, face-to-face with the physician responsible for the patient. Patients were recruited during a 2-week period in 2023 (8–21 May), and a 1-week period in 2018 (12–18 March) and 2019 (4–10 March). The study protocol was disseminated to all investigators in all three study editions (see Appendix), and was explained to them via a general teleconference and then questions were answered via email or telephone by three of the authors: GP, JRP-P, and JMC. Data collection was carried out in an electronic case report form by two researchers from each centre as mentioned above. Data validation was performed centrally by GP and JMC, by reviewing the data collected in each hospital. GP and JMC issued queries and requests for missing data until the database was closed.

Subjects

In each hospital, MDRO sampling was performed on all clinical specimens submitted for diagnosis of infection from patients admitted to any of the inpatient units of the hospital during the study period.

Only patients with MDRO infections were included in this study. In patients who had more than one episode of MDRO infection, it was recorded only when it was caused by a different MDRO than the one causing the previous episode. Patients with MDRO infection were followed until 30 days from the day of diagnostic sampling. MDRO isolated from surveillance screening samples or from clinical samples that were considered contamination or colonisation by the physician in charge of the patient, and those registered for a previous infection with the same MDRO during the study period were excluded. The cases of MDRO infection collected in this study only included those with a confirmed microbiological diagnosis. Potential cases of MDRO infection that were not sampled or were negative were not included.

Variables and definitions

Ten MDRO were considered: methicillin-resistant *Staphylococcus aureus* (MRSA); ampicillin-resistant *Enterococcus* spp, (ARE); vancomycin-resistant *Enterococcus* spp. (VRE); extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL-EC); ESBL-producing *Klebsiella pneumoniae* (ESBL-KP); other ESBL-producing Enterobacterales (ESBL-Other); carbapenem-resistant or carbapenemase-producing *K. pneumoniae* (CR-KP); other carbapenem-resistant or carbapenemase-producing *Enterobacterales* (CPE-Other); *Pseudomonas aeruginosa* (MDR-PA) and *Acinetobacter baumannii* (MDR-AB) resistant to ≥3 classes of antipseudomonal antibiotics or to carbapenem. In addition, we also included *Clostridioides difficile* because of its close association with previous antimicrobial use.

An infection was defined to be caused by multiple MDRO when >1 MDRO was identified in the same clinical specimen. The location/type of infection was defined according to standard clinical criteria together with the sample from which MDRO was isolated as: urinary tract infection; pneumonia; other respiratory infections; intra-abdominal infection; diarrhoea/gastroenteritis; skin and soft tissue infection; surgical site infection; osteoarticular infection; CNS infection; primary bacteraemia or unknown focus; catheter-related bacteraemia; other types of infection. Multifocal or disseminated infections by the same MDRO were recorded as a single case. Nosocomial infection was defined as an infection that occurs 48 h or more after hospital admission and was not present or incubating at the time of admission. Identification and susceptibility testing of MDRO isolates was performed by local laboratories. Breakpoints points used for the definition of resistance were those established by EUCAST.

Demographic/epidemiological (gender, age, type of hospital ward, and nosocomial acquisition), clinical (sample type, site of infection, and mortality), and microbiological variables (MDRO species) were assessed. The number of hospital beds was retrieved from the official registry of the Spanish Ministry of Health. Participating hospitals were classified into four categories: Type I: <200 beds; Type II: 200–499 beds; Type III: 500–999 beds; Type IV ≥1000 beds. The number of hospitals stays (occupied bed days) during the study period was provided by each hospital's administration. Study data were collected and managed in an electronic case report form using REDCap electronic data capture tools hosted at SEIMC.[16,17]

The incidence density of MDRO infections was calculated as the number of new cases of infection occurred during the study period per 1000 hospital stays (occupied bed days) in the same period:

Number of MDRO infections × 1000/total hospital stays.

Mortality was assessed as incidence density calculated as the number of patients diagnosed with an MDRO infection during the study period who died ≤30 days after diagnosis, per 1000 hospital stays (occupied bed days) in the same period, as all-cause 30-day crude mortality:

Number of ≤30-day deaths of patients with MDRO infections × 1000/total hospital stays.

Years of life lost (YLL) were calculated using individual-level data of each patient who died ≤30 days after the MDRO infection diagnosis, by subtracting the patient's age at death from the reference age corresponding to the life expectancy in Spain in 2021 (85.8 years for women and 80.3 for men),[18] and summing the individual YLLs. Only those who died before the reference age are included in the calculation:

$\sum$ *(age at death in years of each patient died ≤30 days after MDRO infection diagnosis–reference age adjusted per sex)*

Statistical analysis and projections

Descriptive statistics were performed to calculate the pooled incidence and mortality rates of MDRO infections. Annual weighted and seasonally adjusted incidence of MDRO infections and number of deaths at all-cause 30-day mortality were estimated. Categorical variables were compared using the Chi-squared statistic with MedCalc v. 22.017. Confidence intervals (95% CI) of the incidence and mortality of MDRO infections were calculated for each hospital category using the Wilson score method and calculated for nationwide projections based on the estimated overall incidence and its standard deviation, with OpenEpi v.3.01. Statistical significance was set at $p < 0.05$.

For countrywide projections, the estimated total number of hospital stays in Spain was calculated considering the total number of hospital beds in the country as per the 2018, 2019 and 2023 data informed by the National Hospital Registries from the Spanish Ministry of Health,[19] and projected in each study replicate as the number of hospital beds in Spain × percentage of daily occupancy recorded in the study period × 365 days.

To control the influence of a seasonal bias in the incidence estimates we performed a previous analysis of the incidence of bacteraemia over five years, 2018–2022, in two of the participating centres, the University Hospital Virgen del Rocio and the University Clinical Hospital of Zaragoza, to calculate the monthly seasonal correction factors (SCF) using SPSS v.29.0.1.0.

To control the representativeness bias per hospital type, we first calculated weights for the four hospital types, dividing the proportion of hospital beds of a hospital type in the sample by the proportion of hospital beds in Spain of the same hospital type. Then we calculated the

Weighted incidence rate as follows:

$\sum$ *((Incidence of MDRO infections per hospital type in the study sample/SCF of the month in which the study was carried out) × hospital type weight))/*$\sum$ *(weights)*

The estimate of number of MDRO infections nationwide for each year was calculated as follows:

Estimated total number of hospital stays in Spain × Weighted incidence rate of MDRO infections/1000

Mortality nationwide was estimated as:

Estimated total number of hospital stays in Spain x Weighted incidence rate of 30-day deaths/1000

Estimated YLL was calculated as:

Estimated mortality nationwide × (Number of YLL/ number of 30-day deaths in the study sample)

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Observed results

A total of 82, 133, and 130 hospitals participated in the 2018, 2019, and 2023 studies respectively, with 42,438, 63,900, and 63,001 beds (Table 1), representing 27%, 40%, and 40% of all the hospital beds in Spain (Tables S1 and S2). During the study period the number of overall hospital stays was 237,253, 330,126 and 596,451 respectively (Table 1) and the number of hospitalised patients was 39,541, 55,021 y 99,408. Hospital types III and IV, which are the largest and most complex centres, had the highest representation, 74% and 91% respectively in 2023 (Table S2). All regions (Autonomous Communities) of the country were involved (Tables S3, S4 and Fig. S1).

During the 2018, 2019, and 2023 studies, a total of 907, 1392, and 2351 episodes of MDRO infection were diagnosed in 852, 1333 and 2307 patients respectively, representing a weighted incidence density of 3.54 (95% CI 2.92–4.17), 5.01 (95% CI 3.95–6.07), 4.41 (95% CI 3.55–5.27) MDRO infections/1000 hospital stays, respectively (Table 2).

In 2023, the median age of patients with MDRO infection was 75 years (interquartile range 62–85; range 0–105), and 54.7% were males (Table S5). The difference in median patient age was 10 years between type I hospitals (80 years; IQR 68–88) and type IV hospitals (70 years; IQR 57–81). Overall, 105 infections with multiple MDRO (4.5%) were detected (Table S6). Up to 44 patients (1.9%) presented >1 episodes of MDRO infection. A total of 1071 episodes were nosocomial (45.6%), which showed a significant reduction compared to previous years (p = 0.013) (Table S7). Most patients were admitted in medical services (67%; 1542/2307) (Table S8). The urinary tract was the most common site of infection (42.7%; 1003/2351) (Table 3). A total of 325 patients (14.1%) had bacteraemia, being the urinary tract the most common source of bacteremic infections (39.1%; 127/325) (Table S9).

In the 2023 study, MDROs were identified in 2487 clinical samples. The most frequent type of sample in which an MDRO was detected was urine (38.4%, 956/2487) (Table S10). In total, 2461 MDRO strains were identified, being ESBL-producing *E. coli* the most common MDRO (25.8%; 636/2461) (Table 4, Table S11). The incidence of ESBL-*E. coli* infections was higher in females (32.1%), whereas the highest incidence in males corresponded to MDR-PA (10.4%) (Table S12). Significant changes in the proportion of the aetiology of MDRO infections in 2023 compared with previous years were observed: MRSA, –2.2% (p = 0.014); MDR-PA, –2.4%; (p = 0.011); and MDR-AB, –1.4% (p < 0.0001); *C. difficile*, +5.2% (p < 0.0001); the others remained stable (Table 4).

Overall, 161 (18.9%), 198 (14.9%) and 352 (15.3%) patients died within 30 days of the onset of infection in

Hospital type	Hospitals		Hospital beds		Hospital stays[a]		Median	Range
	n	%	n	%	n	%		
2018 study								
Total hospitals	82		42,438	100%	237,253		2569	379–8052
H. Type I (<200 beds)	11	13%	1834	4%	7962	3%	586	379–1409
H. Type II (200–499 beds)	30	37%	9897	23%	55,154	23%	1851	825–2976
H. Type III (500–999 beds)	33	40%	19,048	45%	128,234	54%	3912	1525–5386
H. Type IV (≥1000 beds)	8	10%	11,659	27%	45,903	19%	6091	1228–8052
2019 study								
Total hospitals	133		63,900	100%	330,126		2021	25–1395
H. Type I (<200 beds)	29	22%	3756	6%	17,677	5%	610	25–187
H. Type II (200–499 beds)	51	38%	16,927	26%	87,322	26%	1757	200–495
H. Type III (500–999 beds)	40	30%	27,841	44%	148,833	45%	3760	500–964
H. Type IV (≥1000 beds)	13	10%	15,376	24%	76,294	23%	5875	1000–1395
2023 study								
Total hospitals	130		63,001	100%	596,451		3833	75–14,614
H. Type I (<200 beds)	33	25%	4369	7%	34,337	6%	967	75–2214
H. Type II (200–499 beds)	43	33%	14,523	23%	149,221	25%	3669	559–7183
H. Type III (500–999 beds)	44	34%	31,520	50%	305,063	51%	7460	290–11,752
H. Type IV (≥1000 beds)	10	8%	12,589	20%	107,830	18%	11,031	1607–14,614

[a]2019 and 2018 study periods spanned one week. 2023 study period spanned two weeks.

Table 1: **Distribution of hospitals and hospital stays during the three study periods grouped by hospital size.**

Hospital type	MDRO infections	MDRO incidence density	30 d-deaths	30 d-death incidence density
	(n)	(cases per 1000 stays; 95% CI)	(n)	(cases per 1000 stays; 95% CI)
2018 study				
Total hospitals	907	3.54 (2.92–4.17)	161	0.46 (0.16–0.76)
H. Type I (<200 beds)	27	3.39 (2.33–4.93)	3	0.38 (0.13–1.11)
H. Type II (200–499 beds)	244	4.42 (3.90–5.01)	46	0.83 (0.62–1.11)
H. Type III (500–999 beds)	475	3.70 (3.39–4.05)	91	0.71 (0.58–0.87)
H. Type IV (≥1000 beds)	161	3.51 (3.01–4.09)	21	0.46 (0.30–0.70)
2019 study				
Total hospitals	1392	5.01 (3.95–6.07)	198	0.43 (0.17–0.69)
H. Type I (<200 beds)	95	5.37 (4.40–6.57)	6	0.34 (0.16–0.74)
H. Type II (200–499 beds)	358	4.10 (3.70–4.55)	60	0.69 (0.53–0.88)
H. Type III (500–999 beds)	636	4.27 (3.95–4.62)	81	0.54 (0.43–0.68)
H. Type IV (≥1000 beds)	303	3.97 (3.55–4.44)	51	0.67 (0.51–0.88)
2023 study				
Total hospitals	2351	4.41 (3.55–5.27)	352	0.62 (0.52–0.72)
H. Type I (<200 beds)	159	4.63 (3.97–5.41)	22	0.64 (0.42–0.97)
H. Type II (200–499 beds)	629	4.22 (3.90–4.56)	94	0.63 (0.51–0.77)
H. Type III (500–999 beds)	1271	4.17 (3.94–4.40)	193	0.63 (0.55–0.73)
H. Type IV (≥1000 beds)	292	2.71 (2.42–3.04)	43	0.40 (0.29–0.54)

MDRO, multidrug resistant microorganism. 30 d-deaths: deaths at day 30 after diagnosis of MDRO infection. 2019 and 2018 study periods spanned one week. 2023 study period spanned two weeks.

Table 2: **Incidence density of MDRO infections and mortality in the three study periods grouped by hospital size.**

	Type of infection	Mortality rate
	% (n)	% (n)
Urinary tract infection	42.7 (1003)	14.2 (142)
Colitis/diarrhoea	15.8 (372)	12.4 (46)
Skin and soft tissue infection	10.2 (240)	13.3 (32)
Intrabdominal infection	8.7 (205)	16.6 (34)
Surgical site infection	5.7 (134)	5.2 (7)
Pneumonia	5.4 (128)	31.3 (40)
Other respiratory tract infections	3.9 (91)	17.6 (16)
Primary or unknown focus bacteraemia	3.2 (76)	31.6 (24)
Catheter-associated bacteraemia	1.3 (31)	19.4 (6)
Osteoarticular infection	1.3 (31)	6.5 (2)
Endocarditis	0.2 (5)	20.0 (1)
CNS infection	0.1 (3)	0.0 (0)
Other	1.4 (32)	9.4 (3)
Total	100 (2351)	15.0 (352)

Data from the 2023 study.

Table 3: **Type of MDRO infection and associated 30-day mortality.**

the 2018, 2019 and 2023 study periods, respectively (Table S13), representing an incidence of 0.46 (95% CI 0.16–0.76), 0.43 (95% CI 0.17–0.69), 0.62 (95% CI 0.52–0.72) deaths per 1000 stays (Table 2). In the 2023 study, pneumonia was the infection with the highest mortality rate (31.3%; 40/128), followed by primary bacteraemia (31.6%; 24/76) (Table 3). The highest mortality rate occurred in patients admitted in ICU wards (27.8%; 58/209) (Table S8). MDR-AB (35.7%), CPE-Other (23.9%), ESBL-Other (19.7%), and CR-KP (18.6%), were the microorganisms associated with higher mortality rates (Table S14).

Annual nationwide estimations

Projected annual nationwide MDRO infections based on the observed data, weighted by hospital type representativeness and accounting for the seasonal factor correspondent to the month where each study replicate was carried out, were 155,294 (95% CI 127,928–182,569), 210,451 (95% CI 165,963–254,975), and 173,653 (95% CI 139,814–207,258) in 2018, 2019 and 2023, respectively (Fig. S2). Estimated deaths among patients with MDRO infections were 20,065 (95% CI 6938–32,958) in 2018, 17,982 (95% CI 7071–28,700) in 2019, and 24,582 (95% CI 20,461–28,796) in 2023 (Fig. S3). Estimated YLL in patients with MDRO infections were 235,690 (95% CI 81,500–387,125), 198,104 (95% CI 77,901–316,185), and 199,962 (95% CI 166,434–234,241) in 2018, 2019 and 2023, respectively.

Discussion

The cumulative burden of AMR in Spain, as estimated in this study, is very high. According to these projections, in 2023 around 170,000 people would have been diagnosed with MDRO infections, of whom 24,000 would have died within 30 days of diagnosis of infection, causing nearly 200,000 YLL.

These figures are significantly higher than those estimated for 2015 by the Spanish Ministry of Health (3058 deaths) and by the ECDC (41,345 cases and 1899 deaths),[5,9] as well as by the WHO European Region study (6220 deaths for 2019).[7] There are several factors that could explain the higher incidence of MDRO infections in our study.

With regard to the incidence of MDROs, the selection of MDROs was different, and more importantly, our approach to identifying MDRO infections differs from methodologies employed in previous studies.[5–7,9] In the study by Cassini et al.,[5] the most similar to ours, 8 MDRO isolated from blood cultures from hospitalised patients are included, without differentiating whether they are hospital-acquired or not, and they assume that they are all pathogens. For the remaining

samples and types of infection, the authors make estimates using coefficients obtained from the literature. The European Antimicrobial Resistance Collaborators study includes 23 pathogens acquired anywhere, without differentiating between community, healthcare or hospital settings.[7] The observed data come from multiple data sources: research hospitals, surveillance networks, and infection databases maintained by private laboratories and medical technology companies. With these data they make annual projections. In our prospective study we included 11 MDRO. We expanded the definition proposed by Magiorakos et al. to include relevant microorganisms that would need second-line antimicrobial agents, in the same way as MDROs do.[20] Hence, we included ampicillin-resistant *Enterococcus* spp. as these patients cannot be treated with beta-lactams, with vancomycin or linezolid being the drugs of choice, as with MRSA. We also included *C. difficile* as this pathogen, like MDROs, is directly related to previous antimicrobial use. All isolates were collected from any clinical samples from patients hospitalised during sampling, and all isolates underwent individualised microbiological and clinical assessment by the study investigators, establishing in each case whether or not they were true pathogens or contaminants/colonisers, whether or not the infection was hospital-acquired, the type of infection, the site of infection, and the outcome 30 days after diagnosis.

Several factors contribute to the higher MDRO mortality estimated for Spain in our study in 2018, 2019 and 2023 (20,065, 17,982, and 24,582 deaths respectively), compared to that estimated by the two other large population-based studies on the burden of MDRO infections with 1899 attributable deaths in 2015,[5] and 6220 attributable deaths in 2019,[7] neither of which gives 95% CI. Firstly, the higher incidence of MDRO infections in our study, because of the methodological disparities explained above, plays a significant role. Secondly, and notably, the discrepancy in mortality definitions. Both studies used attributable mortality, and we utilized crude mortality, encompassing deaths from any cause within 30 days of infection diagnosis. Measuring attributable mortality requires the collection of all variables representing the main prognostic factors, to perform a multivariate analysis and then, the analysis of attributable mortality as described by the Driving reinvestment in research and development and responsible antibiotic use (DRIVE-AB) Consortium.[14] Using this complex, time-consuming, and resource-intensive methodology to determine the attributable mortality of an infection is feasible in clinical studies with 1276 or 1175 patients,[21,22] but hardly feasible in population-based studies such as ours with 39,541, 55,021, and 99,408 patients respectively. In fact, in the population-based studies on AMR in which attributable mortality has been measured, this is not done following the method described above,[14] not even on the observed data, but is calculated using coefficients obtained from the literature search.[5,7] Because of these differences in mortality definition and design, the estimated annual results are very different. It is worth noting that in the 2019 population-based study,[7] they also estimate mortality associated with MDRO infections, and it was 27,300 deaths, higher than the 17,982 deaths (95% CI 7071–28,700) estimated in our study for the same year. In 2015, the Ministry of Health estimated that 3058 deaths in Spain were linked to MDRO infections in a study using hospital discharge reports from 300 hospitals.[9] However, those reports rely on ICD9M coding,[23,24] which categorizes only MRSA, VRE, and *C. difficile* as MDRO, significantly impairing the sensitivity of this MDRO infection registry.

Thanks to the microbiological diagnosis and clinical follow-up of each patient, our study yields the following clinical information of interest on MDRO infections. It shows that urinary tract infection is the most common (42.7%), and that ESBL-producing *E. coli* is the most frequent MDRO (25.8%) in hospitalised patient infections in Spain. The incidence of ESBL-*E. coli* infections was higher in females (32.1%), whereas the highest incidence in males corresponded to MDR-PA (10.4%). This distribution is in line with that described in a European prevalence study on bacteraemia.[25] During the study period, the incidence of most MDRO remained stable, except for *C. difficile* which increased (+5.2%), and MRSA (–2.2%), MDR-PA

MDRO	2018	2019	2023	2018 vs. 2019	2018 vs. 2023	2019 vs. 2023
	% (n)	% (n)	% (n)	p-value	p-value	p-value
ESBL-EC	25.5 (231)	25.7 (385)	25.8 (636)	0.88	0.85	0.94
ARE	17.2 (156)	15.2 (228)	16.0 (393)	0.20	0.43	0.54
C. diff.	10.4 (94)	9.9 (148)	15.1 (372)	0.71	0.0007	<0.0001
ESBL-KP	9.2 (83)	13.3 (199)	12.9 (317)	0.002	0.004	0.70
MRSA	14.3 (130)	15.0 (224)	12.2 (301)	0.67	0.13	0.014
MDR-PA	11.4 (103)	10.0 (149)	7.6 (188)	0.28	0.001	0.011
CR-KP	3.9 (35)	3.7 (56)	4.6 (113)	0.89	0.37	0.20
ESBL-Other	2.1 (19)	2.7 (41)	2.5 (61)	0.33	0.53	0.61
CPE-Other	2.2 (20)	1.5 (22)	1.9 (46)	0.18	0.54	0.35
VRE	1.0 (9)	1.0 (14)	0.8 (20)	0.89	0.61	0.68
MDR-AB	3.0 (27)	2.0 (30)	0.6 (14)	0.13	<0.0001	<0.0001
Total	100 (907)	100 (1496)	100 (2461)	–	–	–

MDRO, multidrug resistant microorganism; ESBL-EC, Extended spectrum beta-lactamase-producing *Escherichia coli*; ARE, Ampicillin-resistant *Enterococcus* spp.; C. diff., *Clostridioides difficile*; ESBL-KP, ESBL-producing *Klebsiella pneumoniae*; MRSA, Methicillin-resistant *Staphylococcus aureus*; MDR-PA, *Pseudomonas aeruginosa* resistant to at least three antibiotic classes or to carbapenems; CR-KP, Carbapenem-resistant or carbapenemase-producing *K. pneumoniae*; ESBL-Other, Other ESBL-producing *Enterobacterales*; CPE-Other, Other carbapenem-resistant or carbapenemase-producing *Enterobacterales*; VRE, Vancomycin-resistant Enterococcus spp.; MDR-AB, *Acinetobacter baumannii* resistant to at least three antibiotic classes or to carbapenem. The breakpoints used for the definition of the resistance phenotypes were those established by EUCAST. 2019 and 2018 study periods spanned one week. 2023 study period spanned two weeks.

Table 4: **Breakdown of MDRO infective isolates in the three studies.**

(–2.4%) and MDR-AB (–1.4%) which decreased significantly (Table 4). Understanding the factors that might have influenced these variations requires a different study design than that of the present study. But the downward trend observed in recent years in the number of infections caused by MRSA, MDR-PA, and MDR-AB,[26–28] and the increase in CD infections after the COVID-19 pandemic have been previously described.[29,30]

Our findings for 2023 show that less than 50% MDRO infections (45.6%), are hospital-acquired, and how this trend is decreasing throughout the study, thus underlining the importance of MDRO in healthcare-associated and community-acquired infections. This change could be explained by the reduction in nosocomial infections in recent years, attributed to improvements in infection prevention and control strategies.[31] Moreover, because the 2023 study was conducted in May, when the flu epidemic, which is associated with a higher frequency of nosocomial infections, had already ended.[32]

Finally, the overall all-cause mortality 30 days after diagnosis of a MDRO infection was high (14.9–18.9%). Mortality was highest in patients with pneumonia (31.3%) and in infections caused by MDR-AB (35.7%), CPE-Other (23.9%), ESBL-Other (19.7%), and CR-KP (18.6%). It is not possible to compare these clinical data with other studies because the afore mentioned studies related to the burden of MDRO infections lack this information.

Our study has several limitations, with the most significant being that the annual incidence and mortality data for MDRO infections in Spain are extrapolations derived from real data collected over two weeks in 2023, representing 3.8% of the year, and from 130 hospitals, constituting 40% of the hospital beds in the country, with the consequent bias due to the risk of under-representation and seasonal influence. The length of the sampling period of one or two weeks was an empirical decision because we found no studies with a design like ours to take as a reference. The sampling duration of the study by Cassini et al.,[5] the most similar to ours, is much longer: one year vs. one or two weeks in ours. In contrast, in our study, the representativeness of the participating hospitals is higher, 82, 133 and 130 respectively vs. 44 Spanish centres for which the number of beds and regional distribution is unknown.[5] It should be noted that ECDC ranks the 44 Spanish hospitals participating in the EARS-Net database, which feeds that study,[5] as a high hospital representativeness for Spain.[33] The same institution, ECDC, in the study 'Point Prevalence Survey of Healthcare-Associated Infections and antimicrobial use in European acute care hospitals 2022–2023',[34] recommends a sample size between 10,000 and 23,000 patients from a sample of 25–60 hospitals, depending on the average size of hospitals in the country. These figures are exceeded in our study, both in the number of patients analysed during sampling, which was 39,541, 55,021, and 99,408, and in the number of centres, which was 82, 133 and 130 respectively. The voluntary participation in the study explains that not 100% of the hospitals in the country were included, but only those that accepted the invitation to participate as stated in Methods. However, this limitation is at the same time a strength because, thanks to the commitment of the researchers in each centre, it has been possible to carry out this academic study.

The seasonal influence bias is real. Different studies confirm the seasonal influence on hospital-acquired and MDRO infections although with contradictory results, probably because the factors determining it are numerous, dynamic, and therefore difficult to measure. In a study carried out in hospitalized patients in the United States 2013–2017, the authors found that MDR Enterobacteriaceae and MDR *Acinetobacter* spp. were more common in winter.[35] In contrast, in another national study in Belgium, the peak incidence of gram-negative bacterial infections in hospitalised patients, including MDROs, was reported to be in summer.[36] To control for seasonality bias in our study, we conducted a five-year retrospective study in two geographically distant participating hospitals (one Type III in the North and one Type IV in the South of Spain) to determine the influence of seasonality on the annual distribution of MDRO bacteraemia, confirming that the incidence varies depending on the season, and thus calculating the monthly seasonal factor to apply to the calculation of annual estimates for the three study replicates.

Another limitation of the study is the utilization of crude mortality as a metric to define the outcome of MDRO infections, as it precludes the determination of mortality specifically attributable to these infections. We chose crude mortality as an indicator to measure outcome after MDRO infection for pragmatic reasons. We have mentioned above the difficulty of measuring attributable mortality as described by the DRIVE-AB Consortium[14] in large population-based studies, to which must be added the limitations of doing so with estimated projections from studies using big data from multiple sources and very little directly observed data.[5,7] The crude mortality indicator has the advantage that its measurement is unbiased. This objectiveness in the assessment is important because of the actual difficulty in deciding whether the death of a patient with MDRO is due to the infection or not. The consistency of the crude mortality data is reflected in the fact that the estimated results for the three years of the study have been comparable.

The non-inclusion of infections caused by antimicrobial-susceptible bacteria precludes knowing the magnitude of the health consequences of these infections and calculating attributable mortality as discussed above. These infections were not included in the study design because they are not the aim of the study, which has focused exclusively on infections caused by MDRO.

Another limitation of this study is that antimicrobial consumption and prescription profile, both of which are related to the incidence and outcome of MDRO infections, have not been analysed.

Finally, the results of this study are focused on MDRO infections in hospitalised patients and are therefore not valid for MDRO infections in outpatients, nor in nursing homes and other non-hospital settings, which are of great importance in Spain, taking into account that the prevalence of MDROs in residents in these facilities is high[37] and that the number of beds in these facilities, 393,581, far exceeds the number of hospital beds.[38] Future research could aim to expand the scope to include non-hospitalised populations.

This study has several methodological strengths that enhance the validity and reliability of its conclusions. The identification of patients with MDRO infection was performed prospectively based on the routine microbiological diagnosis in clinical samples established in the microbiology laboratory of each centre. Importantly, MDRO sampling was performed on all samples submitted for microbiological diagnosis of infection in patients admitted to any of the hospital wards; and each of these patients with MDRO isolates was evaluated by a clinical investigator to rule out colonisation and followed up for 30 days, increasing the sensitivity and specificity of the results with both interventions. Neither of the two large population-based studies cited above measured this variable.[5,7]

The national representativeness of the study is high as commented previously.[5,33,34] It should be noted that the representativeness in terms of hospital beds in the country rises to 74% and 91% in Type III and IV hospitals respectively, the largest and most complex centres, and also that all of the 17 autonomous communities of the country are represented, which is of interest because they have their own healthcare systems.

Finally, the study has been replicated on the three foreseen occasions and the results have been comparable, reflecting its feasibility and consistency.

We hope that these results will help to reinforce awareness that AMR is a major threat to global public health, which requires commitment at local, national, and international levels to identify priorities, formulate targeted and well-funded policies, and drive research for the optimisation of antimicrobial use.[39] The time-efficient methodology of this study could be useful to measure the health burden of MDRO infections in other European countries and to compare results.

Conclusion

According to the results of this study, the disease burden of MDRO infections in Spain is significantly higher than expected. Nationwide actions need to be intensified to combat AMR. These results can help raise awareness among health professionals, the media, citizens, and health authorities, on the fact that AMR is a real threat. The time-efficient methodology of this study could be useful to measure the health burden of MDROs in other European countries and to compare outcomes.

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Data sharing statement

All data were de-identified by each participating hospital and linked and accessed through a secure server at the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). The data that support the findings of this study are available, anonymised, from the corresponding author, JMC, on reasonable request, after an agreement with SEIMC had been signed.

Ethical statement

Study approval was granted by the Internal Review Board of the University Hospitals Virgen Macarena and Virgen del Rocío (Exp. 2018/072). Informed consent was waived. Following Spanish legislation, administrative hospital approval was requested before enrolment.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101220.

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